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ORIGINAL ARTICLE

Predictive parameters for the clinical course of Crohn's disease: development of a simple and reliable risk model

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Abstract

Purpose The aim of our study was to identify clinical parameters in recently diagnosed Crohn's disease (CD) patients for prediction of their disease course.

Methods EPIC (Early Predictive parameters of Immunosuppressive therapy in Crohn's disease) is a prospective, observational study in 341 patients with a recent CD diagnosis (≤ 6 months), and naïve to immunosuppressants (IS) and anti-tumor necrosis factor α (TNF) agents. Patient characteristics were documented up to 2 years. In line with national and international guidelines, a complicated disease course was defined as need for immunosuppressants and/or anti-TNF agents, and CD-related hospitalization with or without immunosuppressants and/or anti-TNF agents.

Results A total of 212 CD patients were analyzed of whom 57 (27%) had an uncomplicated disease within 24 months, while 155 (73%) had a complicated disease course: need for IS and/or anti-TNF agents ($N = 115$), CD-related hospitalization with or without IS/anti-TNF agents ($N = 40$). Identified risk predictors for a complicated disease were as follows: age at onset < 40 years (OR 2.3; 95% CI 1.2–4.5), anemia (OR 2.1; 95% CI 1.1–4.2), and treatment with systemic corticosteroids at first flare (OR 2.2; 95% CI 1.1–4.7). These three parameters were used to develop a risk model allowing prediction of the future disease course.

Conclusion Our three-parameter model enables an assessment of each CD patient's risk to develop a complicated disease course. Due to the easy accessibility of these parameters, this model can be utilized in daily clinical care to assist selecting the initial treatment for each individual patient.

Keywords Crohn's disease · Predictors · Immunosuppressive therapy · Anti-TNF therapy · Disease course

Introduction

The clinical course of CD is highly variable and ranges from a single episode to a potentially life-threatening continuous disease [1, 2]. Population-based studies have shown that the majority of patients (55%) have moderate disease activity within 5 years after diagnosis, whereas 25% experience disease worsening [3].

Andreas Stallmach and Bernd Bokemeyer contributed equally to this work.

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At present, different treatment strategies are discussed in early CD: (1) the conventional step-up approach (incremental intensification of treatment)—corticosteroids, followed by immunosuppressants in combination with a tapering course of corticosteroids and finally anti-TNF agents; and (2) the top-down strategy characterized by an early use of anti-TNF agents as monotherapy or in combination with IS [4]. The treatment objective should include steroid-free clinical remission, mucosal healing, prevention of complications, disability, and surgery as well as an improvement of quality of life [4, 5]. In order to avoid long-term systemic corticosteroid (SCS) therapy, initiation of IS/anti-TNF agents should be considered early, especially in patients with predictors of an unfavorable disease course [6, 7]. Therefore, it is crucial to identify patients at high risk for developing a complicated course early after diagnosis, in order to immediately initiate an appropriate immunosuppressive therapy [6, 7].

In the past, several studies were published in order to identify parameters for the individual prediction of disease course. An age below 40 years, the presence of perianal disease, and the initial requirement for corticosteroids at first diagnosis were identified as predictive factors for a subsequent disabling disease course [8]. The results of all these studies, reviewed by Torres et al. [9], suggest that beyond phenotypic characteristics (e.g., age, extent of the disease, complications) [1, 2, 8, 10–21], symptoms and clinical constellations (e.g., weight reduction, fever, or smoking) [10, 12, 13], laboratory and imaging results (e.g., CRP level, platelet count, or endoscopic features) [12, 13, 22, 23], and genetic markers (e.g., nucleotide-binding oligomerization domain (NOD) 2 mutations) [24] have some predictive value. In a retrospective pilot study, we identified three independent predictive parameters: age at diagnosis below 40, male gender, and the need for SCS therapy at first diagnosis [21]. Here, we describe the results of the subsequent prospective study (EPIC), which was conducted to confirm the predictive value of these retrospectively identified parameters. By use of these predictors, a simple and reliable risk model for early risk stratification for a complicated course of CD was developed with a particular focus on parameters readily accessible without special diagnostic requirements useful for daily clinical practice.

Materials and methods

Study conduct

The EPIC study is a prospective, observational study, performed from April 2010 until June 2015 at 70 German inflammatory bowel disease (IBD)-specialized centers representing different care levels including both outpatient and inpatient care. The primary endpoint was the proportion of patients who had a complicated CD course and this was defined as necessity of treatment with conventional IS (azathioprine, methotrexate, 6-mercaptopurine) and/or anti-TNF agents (adalimumab, infliximab) [6, 21] within 24 months from baseline. The secondary endpoint was the proportion of patients who were CD-related hospitalized [7] with or without IS/anti-TNF agent within the study period. Baseline demographic data (e.g., age, age at diagnosis, body mass index (BMI), duration of disease, gender) and smoking status (smokers, ex-smokers and non-smoking, specifying the duration of smoking) were determined. Furthermore, the family history, CD-related extraintestinal manifestations (EIM) like pyoderma gangrenosum, erythema nodosum, uveitis/iritis, arthralgia, ankylosing spondylitis, arthritis and primary sclerosing cholangitis, and disease location and symptoms (inflammatory stricture, number of cutaneous draining and internal fistulas, abdominal mass, rectal bleeding, anemia, fever, and fatigue) at diagnosis were analyzed, as well as previous and current CD medication. Changes in medication and a physical examination, including all mentioned parameters above at baseline, were performed at each visit. The time interval until the need for IS/anti-TNF therapy or CD-related hospitalization was documented.

Patients were followed up for 24 months or until the primary endpoint has been met. Up to 6 visits were scheduled: baseline, and after 3, 6, 12, 18, and 24 months, respectively.

Patient population

Patients with a recent diagnosis of active CD (≤ 6 months before baseline visit) without a stricturing or penetrating disease course, ≥ 18 years of age, and naïve to conventional IS (thiopurines, methotrexate, calcineurin inhibitors) and anti-TNF agents (adalimumab, infliximab) at baseline were consecutively enrolled. Written informed consent was obtained from each patient included in the study.

Statistical analysis

The univariate influence of different predictive parameters for the risk of an IS/anti-TNF therapy or a CD-related hospitalization with or without IS/anti-TNF was analyzed using a logistic regression analysis. Since the effect of one parameter may be influenced by other parameters, a multivariate regression analysis was performed, additionally.

Subsequently, all parameters inclusive of the interaction terms were included in a full multivariate model. Based on the results of the univariate and multivariate analyses, all factors were examined in the final model in which the p value of the coefficient estimator of the respective parameters determined by the Wald chi^2 test was below the value 0.05.

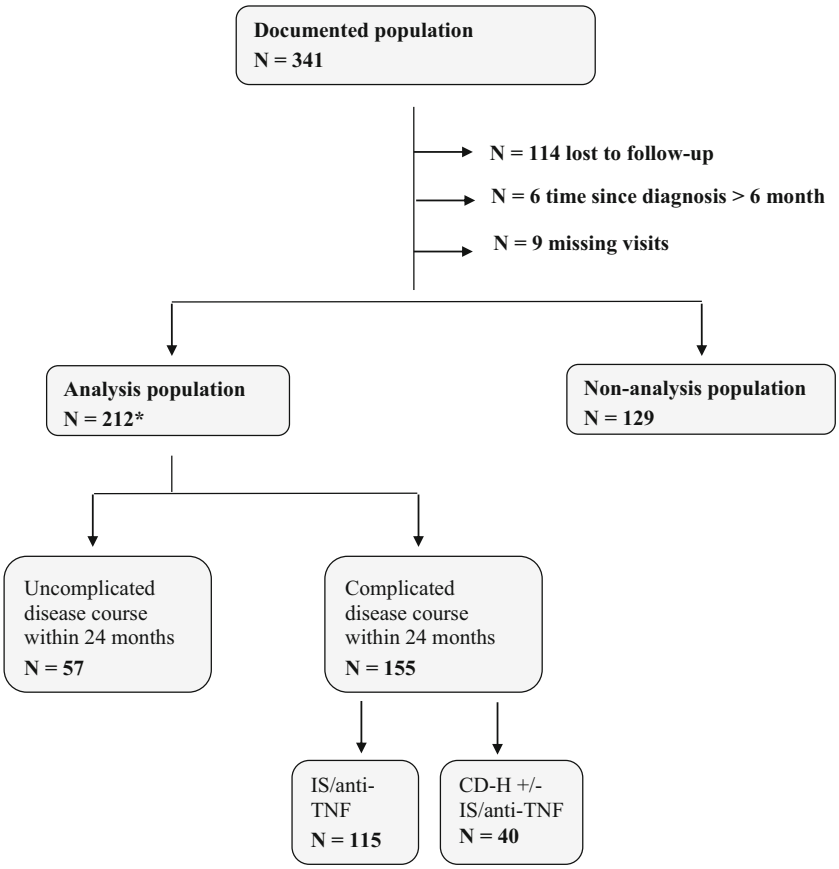

Fig. 1 Patient disposition and analysis population. The asterisk indicates that multivariate analysis was performed for $N = 211$ patients, because for $N = 1$ patient within the analysis population data was missing. CD-H = patients who were CD-related hospitalized; IS/anti-TNF = patients who needed immunosuppressant and/or anti-TNF agent; ± = with or without

Through stepwise forward selection, only the statistically significant factors remained in the optimized final model ($p < 0.05$).

Results

Patient characteristics

In total, 341 patients with a recent diagnosis of CD (≤ 6 months) were enrolled. A total of 114 were lost to follow-up; for 9 patients, visits were missing and 6 patients did not meet the inclusion criteria, due to disease duration >6 months. Therefore, the analysis population consisted of 212 patients with a complete follow-up. Within the analysis population, 26.9% (57/212) of the patients showed an uncomplicated disease course over the entire study period; 54.2% (115/212) needed an immunosuppressive therapy (IS/anti-TNF) and 18.9% (40/212) were CD-related hospitalized (CD-H) with or without IS/anti-TNF (these patients met one study endpoint and were documented no further) (Fig. 1).

Table 1 Demographic data of analysis population at baseline

	Mean	Median	SD	Min	Max
Age (years) ($N = 211$)	32.7	28.9	12.8	16.0	77.9
Age at first diagnosis (years) ($N = 211$)	32.6	28.8	12.8	16.0	76.9
Duration of disease (months) ($N = 212$)	1.51	0.98	1.45	0.0	5.82
- BMI ($N = 206$)	23.6	22.6	4.86	14.5	46.3
- Weight (kg) ($N = 206$)	70.4	70.0	15.9	46.0	150.0
- Smoking status (years)					
- Smoker since (years) ($N = 63$)	13.4	11.0	9.75	1.0	50.0
- Ex-smoker since (years) ($N = 31$)	5.48	2.0	9.38	0.0	44.0

Mean and median values of baseline characteristics for N patients within the analysis population

SD, standard deviation; *Min*, lowest value; *Max*, highest value

Table 2 Modified Montreal classification of analysis population

Age at diagnosis (*N*, (%))	A1 ≤ 16 years	1 (0.5)
	A2 ≥ 17–≤ 40 years	154 (72.6)
	A3 > 40 years	56 (26.4)
	No information	1 (0.5)
Location (*N*, (%))	L1 ileal*	42 (19.8)
	L2 colonic	112 (52.8)
	L3 ileocolonic	159 (75.0)
	L4 isolated upper disease	33 (15.6)
	Anal/perianal	17 (8.0)
Behavior (*N*, (%))	Stenosis	39 (18.4)
	Fistulas	11 (5.2)

*L1 ileal: ileal and jejunal disease location, patients with structuring and penetrating disease course were excluded from the study

Baseline characteristics of the analysis population are shown in Table 1. The mean age was 32.7 years (standard deviation (SD) 12.8) with a mean age at diagnosis of 32.6 years (SD 12.8). The mean time of disease duration until inclusion into the study was 1.5 months (SD 1.45).

A modified Montreal classification was used to describe the disease extent of the analysis population, because patients with a structuring and/or penetrating disease course were excluded from the study (see Table 2).

Observation of the disease course

After 3 months and at all following visits, the absence or presence of IS/anti-TNF was documented. A detailed course of the medication is summarized in the supplemental material (see supplemental figure 1). Due to the fact that a small number of patients received an IS or anti-TNF therapy, both groups were summarized together for further analysis.

No patient received 6-mercaptopurine or a calcineurin inhibitor during the study period.

Of the patients with need for IS/anti-TNF (115/212), 79.1% (91/115) were at age < 40 years, 73.9% (85/115) had an ileocolonic pattern of disease, 4.3% (5/115) had an EIM affecting the skin, and 21.7% (25/115) affecting the joints. In total, 55.7% (64/115) needed SCS for the first flare and 3.5% (4/115) showed no response to SCS.

In addition to the need for IS/anti-TNF, it was assessed how many patients had a CD-related hospitalization during the study. In total, 18.9% (40/212) of the patients were hospitalized and follow-up was stopped for these patients. Within this population, 75% (30/40) were at age < 40 years, with ileocolonic pattern of disease 70.0% (28/40). In total, 7.5% (3/40) and 17.5% (7/40) had an EIM affecting skin and joints, respectively. And 50% (20/40) required SCS at first flare and only one patient showed no response to SCS.

The median time until the patients needed an IS/anti-TNF and/or were CD-related hospitalized was 4.2 months (range 0.4–26.1 months). No statistical difference in baseline characteristics between the groups could be observed (see Table 3).

Predictive parameters for a complicated disease course

In order to identify parameters predictive for risk stratification, we performed uni- and multivariate logistic regression analyses. The results are provided in Table 4.

Based on these results, only those factors were included in a reduced risk model, which were statistically significant at $p < 0.05$ (age at diagnosis < 40 years, anemia, SCS therapy at first flare, and an increased CRP level) except for abdominal mass, which seems to be multi-collinear with at least 2 other parameters and therefore was excluded from further analysis (data not shown). Parameters being furthermore statistically significant in the reduced risk model were stepwise selected for the optimized risk model. The following factors remained statistically different between groups in the optimized model: age at diagnosis < 40 years, anemia, and SCS therapy at first flare (Table 5).

Based on these three parameters, we developed a predictive risk model allowing the determination of the individual patient's probability for experiencing a complicated disease course (Table 6).

According to this risk model, patients negative for all three predictive parameters have a risk of 8.9% for a complicated disease course. Having one predictive parameter increases the

Table 3 Months until primary and/or secondary endpoints were met

	N		Mean	Median	SD	Min.	Max.
	Valid	Miss.					
Overall (*N* = 155)	154	1	6.9	4.2	5.8	0.4	26.1
IS/anti-TNF (prim. endpoint) (*N* = 115)	114	1	6.8	4.0	5.9	0.4	26.1
CD-H ± IS/anti-TNF (sec. endpoint) (*N* = 40)	40	0	7.2	5.2	5.5	1.5	23.5

Mean and median values of time until need for IS/anti-TNF therapy or CD-related hospitalization with or without IS/anti-TNF therapy for *N* patients

Miss., data missing for *N* patients within the analysis population; *SD*, standard deviation; *Min*, lowest value; *Max*, highest value

Table 4 Risk parameters in the analysis population

	Patients with uncomplicated disease course ($N = 57$)	Patients with complicated disease course ($N = 155$)	Univariate analysis ($N = 212$)		Multivariate analysis ($N = 211$)		
Parameter at baseline	*N* (%)	*N* (%)	OR	*P* value	OR	95% CI	*P* value
Age at diagnosis < 40 years ($N = 211$)	34 (59.6)	121 (78.1)	2.3	0.013	2.4	1.15–4.91	0.019
Male gender	21 (36.8)	65 (41.9)	1.2	0.503	1.3	0.68–2.68	0.395
Smoker/ex-smoker < 3 years	26 (45.6)	60 (38.7)	0.8	0.365	0.8	0.40–1.50	0.444
Manifestation in upper GI tract	7 (12.3)	26 (16.8)	1.4	0.425	1.2	0.47–3.30	0.495
Anal/perianal disease	3 (5.3)	14 (9.0)	1.8	0.376	1.8	0.47–7.07	0.398
Stenosis	9 (15.8)	30 (19.4)	1.3	0.553	1.0	0.39–2.61	0.979
Abdominal mass	4 (7.0)	35 (22.6)	3.9	0.014	3.4	1.06–10.6	0.039
Anemia	15 (26.3)	68 (43.9)	2.2	0.022	1.9	0.87–3.95	0.111
Increased CRP level	32 (56.1)	113 (72.9)	2.1	0.021	1.4	0.70–2.91	0.325
Fever	7 (12.3)	19 (12.3)	1.0	0.996	0.6	0.21–1.73	0.345
Extraintestinal manifestation	11 (19.3)	35 (22.6)	1.2	0.608	1.4	0.59–3.30	0.451
Systemic corticosteroids	12 (21.1)	59 (38.1)	2.3	0.022	1.9	0.88–4.19	0.100

Number of patients with no disease progression (uncomplicated disease course) and patients with complicated disease course (need for IS/anti-TNF therapy and/or CD-related hospitalization during study). The respective parameter at baseline within the analysis population and the odds ratio for each parameter in univariate and multivariate analyses are shown

OR, odds ratio; *95% CI*, confidence interval (95% of values are within this scope)

risk for a complicated disease course already to 66–68%, while having two positive predictive parameters the risk ranged from 81 to 83%. Patients positive for all three predictive parameters have a risk of 91.1% for a complicated disease course. Applied to our cohort of 212 patients, we identified the following statistical parameters for our risk model: sensitivity 77.7% (CI 69.2–84.8%), specificity 100% (CI 96.0–100), positive predictive value 100% (CI 96.2–100), negative predictive value 77.1% (CI 68.5–84.4), and accuracy 87.3%, respectively.

Discussion

EPIC was a prospective study including a large cohort of adults with a recent diagnosis of CD. The aim of this study was to identify reliable clinical predictors of disease worsening, which are easy to assess immediately after CD diagnosis. With 73% of the patients having a complicated disease course, this proportion was higher than anticipated. As the most substantial result, we identified an age below 40 years at disease onset, the early need for treatment with SCS at the first flare and anemia as predictors for a complicated disease course. Two of these clinical predictors (< 40 years of age and need for SCS at diagnosis) were also identified by Beaugerie et al. [8]. Billiet and coworkers summarized that an early need for SCS and age < 40 years at onset were clinical predictors of an unfavorable CD course in 5 of 11 and 6 of 11 studies, respectively [25]. However, the differences

Table 5 Optimized model of predictive risk parameters in the analysis population

Parameter	Multivariate analysis ($N = 211$)		
	OR	95% CI	*P* value
Age at diagnosis < 40 years	2.3	1.2–4.5	0.016
Anemia	2.1	1.1–4.2	0.032
Systemic corticosteroids	2.2	1.1–4.7	0.031

Odds ratio for each parameter in univariate and multivariate analysis are shown. Parameters with a $p < 0.05$ were significant

OR, odds ratio; *95% CI*, confidence interval (95% of values are within this scope)

Table 6 Risk model for prediction of an uncomplicated or complicated disease course

Age at diagnosis < 40 years	Anemia	Systemic corticosteroids	Probability (%)
No	No	No	8.9
No	No	Yes	67.7
No	Yes	No	66.5
No	Yes	Yes	81.6
Yes	No	No	68.3
Yes	No	Yes	82.8
Yes	Yes	No	82.0
Yes	Yes	Yes	91.1

Probability to develop an uncomplicated or complicated disease course (need for IS/anti-TNF agent and/or CD-related hospitalization) for patients with or without the respective parameters

between the studies made it difficult to compare the value of the respective predictive parameters. In contrast, a study with 162 newly diagnosed CD patients aimed identifying baseline factors that predict a mild course of CD and led to the design of a predictive scoring system based on age, CRP, endoscopic severity (adapted Rutgeerts score), perianal lesions, and combined incidence of complications [13]. Additionally, Torres et al. reviewed all predictors for different outcomes in CD identified so far and concluded that prospective studies are still required to establish algorithms to reliably predict the risk for disease worsening [9].

To the best of our knowledge, EPIC is the first prospective study that developed a predictive model for CD risk stratification focusing on parameters easily to assess in daily clinical practice very early after diagnosis. According to our risk model, patients presenting with none of the parameters have a risk of less than 10% to develop a complicated disease course. Already, two positive predictive parameters increase the risk to more than 80%, whereas patients fulfilling all parameters have a risk of 91%. In daily clinical practice, it seems mandatory to reliably predict an individual patient's risk to develop a disease worsening (e.g., with a low probability (< 10%) or a high probability (> 80%)). According to this notion, our risk model yielded an excellent accuracy of 87.3% to predict a complicated disease course. Certainly, reliability of our model should be verified in an independent cohort of patients.

Nevertheless, our study has some limitations. First of all, the number of patients analyzed (212/341) was lower than expected due to a high dropout rate. The dropouts might have resulted from a high number of participating centers each contributing a rather small number of patients. A further limitation is that all centers were specialized in IBD. Hence, patients treated by primary care physicians are not covered by this study and we therefore cannot exclude that other predictors may play a role in non-specialized centers. Similar to the study of Beaugerie et al., more than 70% of patients in our cohort reached the defined primary endpoints (need for IS or anti-TNF agents and/or CD-related hospitalization) [8]. Therefore, an overrepresentation of severe cases in a tertiary centers is apparent.

However, to our knowledge, none of the available prospective studies have focused on cohorts with a short latency after CD diagnosis. In EPIC, the mean time since the establishment of CD diagnosis was 1.5 months (SD 1.45) only. Such early predictors for the disease course are of high importance for the development of personalized therapeutic strategies.

In summary, in the current prospective study, we identified age at diagnosis < 40 years, anemia, and SCS therapy at first flare as clinical parameters associated with a complicated course of CD. Our systematic risk assessment can be used in daily clinical practice to facilitate the configuration of individualized treatment strategies and thereby contributes to optimizing the balance between therapeutic efficacy and safety concerns for newly diagnosed CD patients.

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Compliance with ethical standards

Conflict of interest AS has received consulting fees from AbbVie, Astellas, Biogen, Janssen, MSD, Mundipharma, Summit Therapeutics, and Takeda. Financial support for lectures and teaching from AbbVie, Falk Foundation, Janssen, MSD, Mundipharma, and Takeda. Grant and financial support for Research from AbbVie, Pentax, and Olympus.

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IF has received consulting fees from AbbVie.

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SR and DL are AbbVie employees, and may own AbbVie stock or options.

Ethics approval The protocol was approved by the ethics committee of the Friedrich-Schiller-University Jena at the medical faculty (2753-01/10) on January 28, 2010. The study has been performed in accordance with the principles of the Declaration of Helsinki.

Written informed consent was obtained from each patient included in the study.

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